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(54) Title: APOPTOSIS INDUCING AGENTS AND METHODS

(57) Abstract

Methods and compositions are disclosed for inducing differentiation and apoptosis in cells that overexpress Notch proteins. A cell fate determining function of Notch is specifically disrupted at a time when the cell is undergoing differentiation, which causes the cell to undergo apoptosis. The invention includes therapies for tumors that overexpress a Notch protein (such as Notch-1) by inducing differentiation of the cells in the tumor with a differentiation inducing agent, such as HMBA, in combination with an agent that disrupts the function of the Notch protein. At a time during which differentiation has been promoted, and the cell is susceptible to interference with the anti-apoptosis effect of Notch, the function of the Notch protein is disrupted. Disruption of Notch function can be achieved, for example, by a differentiation inducing agent such as HMBA, combined with antibodies that specifically bind to Notch and inactivate it, for example a monoclonal antibody that recognizes Notch-1 EGF-like repeats 11 and 12, such as monoclonal antibodies A6, C11 or F3. Disruption of Notch function can also be achieved by the expression of antisense oligonucleotides that specifically interfere with expression of the Notch protein on the cell, alone or in combination with antineoplastic agents.